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Oshovsky, Gennady V.; Hessen, Bart; Reek, Joost N. H.; de Bruin, Bas

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Electronic Selectivity Tuning in Titanium(III)-Catalyzed Acetylene Cross-Dimerization Reactions

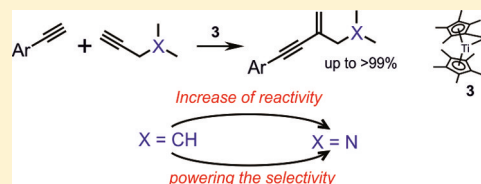
Gennady V. Oshovsky,^{*,†,‡} Bart Hessen,[‡] Joost N. H. Reek,[†] and Bas de Bruin^{*,†}

[†]Supramolecular and Homogeneous Catalysis Group, van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

[‡]Department of Molecular Inorganic Chemistry, Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

Supporting Information

ABSTRACT: The reactivity of open-shell titanium(III) complexes in organometallic catalysis is associated with many open questions, in particular regarding the electronic structure of catalytic intermediates and transition states. The unpaired electron density in principle allows for radical-type reactivity, while at the same time empty d orbitals allow more traditional cis-coordination insertion pathways. In this paper we investigated the $(\text{Cp}^*)_2\text{Ti}^{\text{III}}$ -catalyzed cross-dimerization of aliphatic and aromatic acetylenes, focusing on the reactivity of two different aliphatic acetylenes with a series of different aromatic acetylenes. The applied aliphatic acetylenes **1a** (4-methylpent-1-yne) and **1b** (*N,N*-dimethyl-*N*-propargylamine) have the same size but different electron-accepting abilities. The better π -accepting substrate **1b** shows a higher reactivity and selectivity than substrate **1a** in the studied cross-dimerization reactions. Stronger π back-donation from the titanium-localized SOMO to the substrate thus seems to be a reasonable explanation for the improved selectivity of substrate **1b**. DFT calculations indeed suggest a stronger binding of substrate **1b** as compared to that of **1a** in the selectivity-determining steps of the reaction, thus leading to faster insertions and higher selectivities with substrate **1b**.



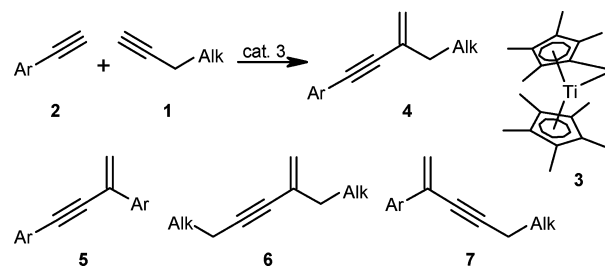
Catalytic organometallic reactions are dominated by the closed-shell reactivity of diamagnetic species.¹ While reports on the open-shell organometallic reactivity of titanium(III) compounds in catalysis dates back to the early era of Ziegler and Natta, our current understanding of these reactions is still rather limited and is associated with many open questions regarding the electronic structure of the catalytic intermediates and transition states. In this perspective we became interested in the catalytic reactivity of $\text{Cp}_2\text{Ti}^{\text{III}}$ -type compounds. While the reactivity of these compounds should in many ways resemble that of their closed-shell $\text{Cp}_2\text{Ti}^{\text{IV}}$ analogues, their unpaired spin density and highly reducing nature also makes them capable of promoting selective radical-type transformations (such as cyclization reactions induced by radical ring opening of epoxides²). We thus wondered if $\text{Cp}_2\text{Ti}^{\text{III}}$ -type compounds have a general preference for radical pathways or perhaps allow a more subtle participation of the singly occupied molecular orbital (SOMO) in tuning the selectivity of catalytic reactions following cis-coordination reactivity. Our interest in SOMO participation in the reactivity and selectivity tuning of catalytic reactions is further inspired by SOMO organocatalysis, which recently opened a new research area.³ For these reasons we decided to study the effect of different substrates on the selectivity of $\text{Cp}^*_2\text{Ti}^{\text{III}}$ -catalyzed cross-dimerization reactions of acetylenes in a combined experimental and computational study.

Selective catalytic dimerization of alkynes is a synthetically useful procedure to obtain enynes,⁴ which are versatile

π -conjugated building blocks in organic synthesis.⁵ The homodimerization reaction has been extensively studied, but the much more challenging selective cross-dimerization of two different alkynes has received much less attention.^{4,6} This is an intrinsically difficult reaction, due to several possible competing reactions leading to regio- and stereoisomers as well as competing cross-dimerization and homodimerization.⁵

The catalyst we used in this study is Ti^{III} complex **3**,⁷ which is an analogue of the Nakamura catalyst ($\text{Cp}^*_2\text{TiCl}_2/\text{Pr}^f\text{MgCl}$).⁴ We used this catalyst for the cross-dimerization between aliphatic **1** and aromatic **2** acetylenes leading to 1,3-enynes (Scheme 1).

Scheme 1. Ti^{III} -Catalyzed Acetylene Head-to-Tail Cross-Dimerization



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Selectivity tuning in homogeneous catalysis generally involves a subtle tuning of steric and electronic factors. Separating steric and electronic influences is not always trivial, and therefore we decided to study the comparative reactivity of the substrates **1a** (4-methylpent-1-yne) and **1b** (*N,N*-dimethyl-*N*-propargylamine) (Figure 1), which have similar steric



Figure 1. Aliphatic acetylenes **1a** and **1b** used in catalytic screening.

features but clearly different electronic properties (see the Supporting Information).⁸

Statistical dimerization would produce the products **4**–**7** in equal amounts (25% each); however, formation of the cross-dimerization products **4** and the homodimerization products **5** is favored due to a significant difference in CH acidity and shape between aromatic and aliphatic acetylenes.⁴ For example, the reaction between **1a** and **2a** leads to a distribution of products in which **4aa** and **5** are clearly favored over **7** (**4aa**, 47%; **5**, 26.5% (Ar = 2-thienyl); **7**, 0%). As a logical consequence of the fact that **2** is consumed more quickly than **1** (due to formation of **5**), a substantial amount of the homodimerization product **6** (26.5% (Alk = Pr-*i*)) is formed as a side product at the end of the reaction.

Comparison of the acetylenes **1a** and **1b** in the Ti^{III}-catalyzed cross-dimerization reactions with the aromatic acetylenes **2a**–**g** (Table 1) revealed a much higher reactivity and selectivity for the nitrogen-containing substrate **1b** in all cases. The reaction with this acetylene is much faster and allows a lower catalyst loading for the reaction to reach completion (for example, the cross-dimerizations with acetylene **1b** need 2 mol % of catalyst **A** to complete the reaction in less than 10 min; under similar conditions, cross-dimerizations with **1a** require 5 mol % of **A** and 1 h reaction time to completion). A detailed kinetic study also demonstrated a clearly higher reactivity of acetylene **1b** compared to that of **1a** (see the Supporting Information).

The higher selectivity of **1b** is best illustrated by the comparative reactions of **1a** and **1b** in the cross-dimerization reaction with 3-thienylacetylene (**2a**). A tremendous improvement of the selectivity is observed for **1b** (from 47% to 93%; see Table 1, entries 1 and 2). The increase in the selectivity is evidenced by ¹H NMR spectroscopy in the range $\delta \sim 5$ –6 ppm showing the 1,3-enyne methylene protons (Figure S9, Supporting Information).

To see whether the Brønsted basicity of the amine in **1b** has any influence on the selectivity, the cross-dimerization between **2a** and **1a** was carried out in the presence of 1.5 equiv of triethylamine or butyldimethylamine (with respect to substrate **1a**). Clearly, this had no positive influence on the selectivity toward cross-dimerization (46–49%, as in the base-free case). This shows that, in contrast with late-transition-metal-catalyzed acetylene cross-dimerization reactions,⁹ the higher basicity of the reaction medium is not responsible for the increased selectivity of **1b** compared to **1a**.

The influence of the change in the reactivity of the aliphatic acetylenes on the improvement of the selectivity can be understood from the reaction mechanism (Scheme 2). DFT calculations at the BP86/def-TZVP level (Table 2) helped us to evaluate and expand the mechanism originally proposed by

Table 1. Results of the Acetylene Cross-Dimerization Reactions

Entry	2	X	4	S, ^a	Yield, ^b
1	 2a	CH	 4aa	47	24
2		N	 4ab	93	90
3	 2b	CH	 4ba	63	45
4		N	 4bb	99	97
5	 2c	CH	 4ca	83	64
6		N	 4cb	99	98
7	 2d	CH	 4da	53	42
8		N	 4db	97	93
9	 2e	CH	 4ea	99	96
10		N	 4eb	>99	98
11	 2f	CH	 4fa	99	96
12		N	 4fb	>99	98
13	 2g	CH	 4ga	99	86
14		N	 4gb	>99	97

^aSelectivity (in C₆D₆), determined from ¹H NMR spectra. ^bIsolated yield (reaction in pentane).

Nakamura.⁴ This study revealed a logical energetic profile and some interesting new catalytic intermediates. The acetylene

Scheme 2. Proposed Mechanisms of the Cross-Dimerization of Acetylenes (R = Alkyl) and Competitive Acetylene Homo-Dimerization (R = Aryl)

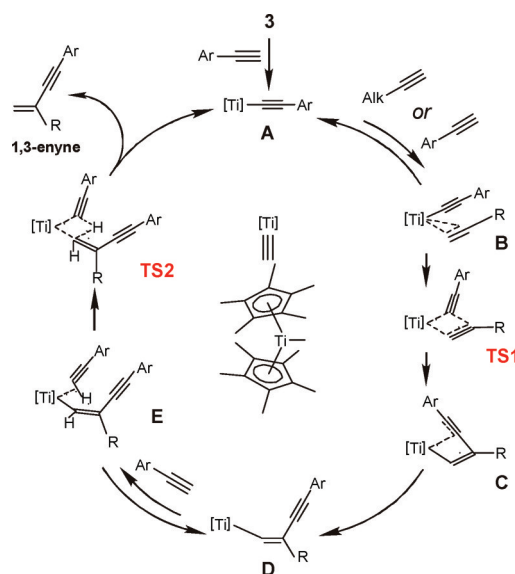


Table 2. Free Energies of the Catalytic Intermediates ($\Delta G^\circ_{298\text{ K}}$, kcal mol⁻¹) on the Basis of DFT Calculations (BP86/def-TZVP)

	2b Ar = Ph			2f Ar = o-Tolyl		
	R = Me ₂ XCH ₂		2b R = Ph	R = Me ₂ XCH ₂		
	1a X = CH	1b X = N		1a X = CH	1b X = N	
A	= 0	= 0	= 0	= 0	= 0	
B	+19.2	+16.2	+18.5	+18.6	+17.6	
TS1	+20.6	+18.4	+22.2	+22.5	+19.4	
C	+7.2	+5.6	—	−3.6	−3.8	
D	−3.8	−4.7	−6.1	−4.5	−4.8	
D	= 0	= 0	—	= 0	= 0	
E	+15.9	+15.1	—	+19.5	+17.3	
TS2	+19.8	+18.4	—	+21.8	+20.2	
A + enyne	−22.5	−23.6	—	−21.4	−22.9	

(cross)-dimerization reaction basically consists of two main processes: acetylene insertion into the Ti–C bond of the acetylide intermediate A (steps A–D) and a σ -bond metathesis process which eliminates the product and regenerates the catalyst (steps D–A).⁸

The reaction starts with the formation of the active catalyst permethyltitanio(III)cene acetylide¹⁰ A from the Ti^{III}-fulvene precatalyst 3 and an acetylenic C–H acid (the typical reaction pathway of the complex 3 with Brønsted acids). The active catalyst A (Scheme 2) then reacts with another acetylene by insertion of the π -cis-coordinated substrate (B) into the Ti–C bond of the acetylide ligand (migratory insertion via transition state TS1) to form C, which rearranges to form the Ti–vinyl derivative D.

Release of the product by net protonation of the Ti–C bond in D by an aromatic acetylene proceeds via formation of the σ complex E followed by σ -bond metathesis (transition state TS2), which regenerates A and completes the catalytic cycle.⁴ Although the calculated spin densities are partly delocalized over their π -conjugated organic ligands, the intermediates B–E are best described as metal-centered radicals (Mulliken spin

densities at Ti >60%). We thus found no indications for any true ligand-radical behavior in the reaction mechanism of this system.

The computed gas-phase free energy profile (Table 2) reveals moderate TS1 and TS2 barriers, in good agreement with relatively fast reactions under the experimental conditions. The σ -bond metathesis half-cycle D–A is always favored by aromatic acetylenes, which are more CH-acidic than the aliphatic species. Therefore, the formation of isomeric acetylene cross-dimer 7 (via the protonation of D by aliphatic acetylenes) is negligible. The formation of aliphatic acetylene homodimer 6, which includes the protonation of complex D by aliphatic acetylenes, is very slow and is only relevant after the complete consumption of the aromatic acetylene.¹¹

Considering the above mechanism, the overall selectivity of the reaction is determined by the relative formation rates of only two species: the acetylene cross-dimer 4 versus aromatic acetylene homodimer 5. This selectivity is determined entirely by the acetylene insertion half-cycle A–D. The TS1 free energy barrier (Table 2) for homocoupling of phenylacetylene 2b is about 2 kcal mol⁻¹ higher than the TS1 barrier for cross-dimerization between 2b and the aliphatic acetylene 1a. This is enough to explain the experimentally observed basic selectivity of 63% (Table 1). Moving from 1a to the more reactive N-acetylene 1b results in a further decrease of the TS1 barrier. Cross-dimerization between 2b and 1b has a roughly 4 kcal mol⁻¹ lower barrier than the homocoupling of phenylacetylene 2b. The DFT data are thus in good agreement with the experimental results and seem to provide a decent explanation for the increased selectivity on going from 1a (63%) to 1b (99%).

The computed higher reactivity of 1b stems from the stabilization of its LUMO (C \equiv C π^* orbital) compared to the higher energy LUMO of 1a (see the Supporting Information). This results in a stronger π coordination of substrate 1b in intermediate B (see Table 2; for a comparison of computed relative bond lengths and bond orders, see Table S2 in the Supporting Information). The different metal–substrate interaction strengths between 1a and 1b in this intermediate appear to be determined by the nature of the SOMO, which mainly reflects the metal to ligand π back-donation component of the Ti–acetylene interaction (Figure 2). The lower energy of

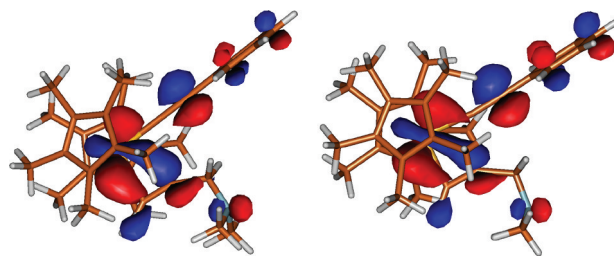


Figure 2. SOMO of intermediate B (left) and transition state TS1 (right) with substrate 1b.

the LUMO of 1b (compared to that of 1a) leads to stronger π back-donation from the Ti-based SOMO in intermediate B and transition state TS1, and this lowers the insertion barrier of substrate 1b as compared to that of 1a (see Figure 2 and Table 2). The unpaired electron in the SOMO of these Ti^{III} catalysts thus seems to be actively involved in tuning the selectivity of these catalytic acetylene dimerization reactions (for an analysis of the

bond lengths, bond orders, and spin densities in **B** and **TS1**, see Tables S1 and S2 in the Supporting Information).

The above electronic effects can be combined with steric tuning to improve the selectivity of the acetylene cross-dimerization reaction further. To demonstrate this, we increased the steric bulk of the aromatic acetylenes **2**. The results are presented in Table 1. A significant improvement of the selectivity is observed, thus providing convenient catalytic routes to a number of synthetically useful 1,3-enynes.¹² The steric effect is most pronounced for the least reactive (and thus initially less selective) substrate **1a**. For example, in the case of the nonbulky phenylacetylenes **2b–d** cross-dimerization with **1a** leads to a moderate selectivity in the range between 53 and 83%, while the use of the sterically more demanding *o*-substituted aromatic acetylenes **2e–g** increases the selectivity to 99% (Table 1, entries 9, 11, and 13). Some of these selectivities are almost as high as those obtained in the reactions with acetylene **1b**. However, the cross-dimerization reactions using **1b** are always more selective than those employing **1a** (Table 1, entries 2, 4, 6, 8, 10, 12, and 14), and the combination of steric and electronic effects gives access to almost absolute selectivities in the reactions of **1b** with the bulky acetylenes **2e–g**.

In conclusion, we have shown that the selectivity of the Ti^{III}-catalyzed cross-dimerization of acetylenes can be tuned by subtle electronic effects. In this substrate-directed reaction,¹³ the different electronic properties of the acetylene substrates **1a** (4-methylpent-1-yne) and **1b** (*N,N*-dimethyl-*N*-propargylamine) have a large influence, and the use of **1b** leads to stronger Ti–substrate interactions in the rate- and selectivity-determining steps of the catalytic reaction. This effect seems to be the result of the stabilizing effect of the nitrogen substituent in **1b** on its π^* -antibonding C \equiv C orbitals (lower LUMO energy), thus leading to stronger π back-donation interactions from the titanium-based SOMO. This leads to faster reactions and thus less competition from the homodimerization, resulting in a substantial increase of the selectivity. Using these electronic effects, we obtained the highest levels of selective cross-dimerization reported to date, thus showcasing a promising tool for organic synthesis.

■ ASSOCIATED CONTENT

● Supporting Information

Text, tables, and figures giving experimental and computational details, NMR spectra, and a kinetic study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: G.V.Oshovsky@uva.nl (G.V.O.); B.deBruin@uva.nl (B.d.B.).

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